## REMARKS/ARGUMENTS

Consideration of this Preliminary Amendment is respectfully requested. Product Claims 1-5 have been cancelled. Method Claims 6-10 have been amended to more clearly point out that the method is for blocking apoptosis during preserving and storing a heart awaiting transplantation. Support for the new amendment is found at several places throughout the specification and in particular on page 4.

In the parent application, Claims 1-10 were rejected under 35 U.S.C. § 102(b) as being anticipated by Massoudy *et al.*

A 15 minute interruption of blood flow and reperfusion which Massoudy *et al.* describe in their article, has little or no relationship to the claimed method for blocking apoptosis during preserving and storing a heart. The major alteration in the canine preserved heart at 18 hours is the appearance of apoptotic cells that indicate a programmed cell death and also the reason that permanent damage occurs in the myocardium. This kind of damage is not seen in the Massoudy *et al.* process. Actually, the inventors did not find apoptotic cells in the solutions used in the claimed method until after 12 hours of preservation. Irreversible damage occurs when apoptotic cells are detected at 18 hours. The unique finding is that cyclosporine A prevents apoptosis and therefore prolongs the preservation times to 18 and 24 hours.

Preventing apoptosis has nothing to do with the findings that Massoudy *et al.* mention at this stage with a nitric oxide-dependent mechanism impeded by endothelin. Massoudy *et al.* disclose a reperfusion solution in which cyclosporin A is present in an amount of only 0.8 μM per liter. Furthermore, the Examiner suggests that if "0.8 μm worked, then 2.5 μm would work better for that purpose". The Examiner's theory, while appearing valid, is simply incorrect as taught in the article by E.J. Griffiths, *et al.* (Griffiths EJ, Halestrap AP: Protection by cyclosporine A of ischemia/reperfusion – induced damage in isolated rat hearts, *J Mol Cell Cardiol* 1993; 25:1461-1469) (a copy is enclosed). According to Griffiths *et al.*, using rat hearts with 30 min. ischemia found a protective effect of 0.2 μm cyclosporine A and at 1.0 μm the protective effect was reversed. (*See Abstract and page 1466, right hand column.)* This would suggest two things: (1) that rat hearts or small animal hearts respond differently than large animal models and (2) the short-term ischemia-reperfusion model used in the referenced articles is interacting with cyclosporine A at a different point in the metabolism than in our experiments

at 18 and 24 hours which prevents the formation of apoptotic cells. The mechanism of action of cyclosporine A is via the mitochondrial transition pore being stabilized by the binding of cyclophilin D by cyclosporine A. This in turn keeps ATP from leaving the mitochondria and prevents caspase activation which initiates apoptosis.

Therefore, Massoudy *et al.* cannot anticipate or make obvious the claims as now amended.

Claims 1-10 were also rejected under 35 U.S.C. § 103 as being unpatentable over Raymond ('462), Jurado *et al.* and Massoudy *et al.*

The patent to Raymond is directed to a preservation solution that includes an isotonic solution for perfusing and storing a heart at room temperature for up to at least 24 hours while waiting transplantation. The Raymond preservation solution requires an amiloride-containing compound and a small amount of adenosine. As previously noted, the preservation solution described in Raymond that includes amiloride and adenosine do not prevent ATP loss inhibiting apoptosis as shown by the claimed invention.

The Massoudy *et al.* article does not teach use of amiloride in any type of solution whatsoever in the claimed amount. Massoudy *et al.* deal with a completely different technical problem over the present application, which is to minimize the reperfusion entry following the ischemic event. The teachings of Massoudy *et al.* show that the level of venus NO recovers faster after the ischemic episode and remains stable if the heart is perfused with the isotonic solution comprising cyclosporin A. Massoudy *et al.* is silent about the effects on an isolated heart preserved in the isotonic solutions disclosed in Massoudy *et al.* Thus, departing from Raymond as the primary reference, there is no particular reason for which one skilled in the art would turn to Massoudy *et al.* because Massoudy does not suggest that the isotonic solution therein disclosed would be particularly suited for preserving solutions for a heart awaiting transplantation.

The article to Jurado *et al.* discusses studies that affect the cardiac muscle after heart transplantation and has nothing whatsoever to do with the claimed.

It is, therefore, respectfully submitted that the claims, as amended, are not obvious over Raymond, Jurado *et al.* and Massoudy *et al.* Specifically, none of the three references teach adding cyclosporin A to any kind of solution whatsoever in the amount claimed; Raymond does

not use a cyclosporin, Jurado *et al.* is for treatment after a heart has been transplanted. It is, therefore, respectfully submitted that the cited prior art does not make obvious the solution of Claims 1-2, 4-5 and the process claimed in Claims 6-7 and 9-10.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

Ernest B. Lipscomb, III
Registration No. 24,733

**Customer No. 00826**
**ALSTON & BIRD LLP**
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Charlotte Office (704) 444-1000
Fax Charlotte Office (704) 444-1111
CLT01/4652334v1

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I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on June 15, 2004.

Janet F. Sherrill